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Risk of skin cancer in patients with HIV

a Danish nationwide cohort study

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Published in:

Journal of the American Academy of Dermatology

DOI (link to publication from Publisher):

[10.1016/j.jaad.2018.03.024](https://doi.org/10.1016/j.jaad.2018.03.024)

Publication date:

2018

Document Version

Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Omland, S. H., Ahlström, M. G., Gerstoft, J., Pedersen, G., Mohey, R., Pedersen, C., Kronborg, G., Larsen, C. S., Kvinesdal, B., Gniadecki, R., Obel, N., & Omland, L. H. (2018). Risk of skin cancer in patients with HIV: a Danish nationwide cohort study. *Journal of the American Academy of Dermatology*, 79(4), 689-695. <https://doi.org/10.1016/j.jaad.2018.03.024>

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Accepted Manuscript

Risk of skin cancer in HIV-infected patients: a Danish nationwide cohort study

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PII: S0190-9622(18)30475-4

DOI: [10.1016/j.jaad.2018.03.024](https://doi.org/10.1016/j.jaad.2018.03.024)

Reference: YMJD 12412

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 23 August 2017

Revised Date: 14 March 2018

Accepted Date: 18 March 2018

Please cite this article as: Omland SH, Ahlström MG, Gerstoft J, Pedersen G, Mohey R, Pedersen C, Kronborg G, Larsen CS, Kvinesdal B, Gniadecki R, Obel N, Omland LH, Risk of skin cancer in HIV-infected patients: a Danish nationwide cohort study, *Journal of the American Academy of Dermatology* (2018), doi: 10.1016/j.jaad.2018.03.024.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title

Risk of skin cancer in HIV-infected patients: a Danish nationwide cohort study

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Word count

Abstract: 200

Capsule summary: 60

34 Manuscript: 2502

35 Figures: 2

36 Tables: 3

37 Number of references: 18

38

39 Funding sources: None

40

41 **Conflicts of interest**

42 JG institution have received grants and fees for adboards, teaching and clinical trials from

43 Gilead, BMS, MSD, Janssen, Medivir, and ViiV.

44 MA has received travel grants from GSK and Janssen

45 RM travel to scientific meetings has been funded by the medical industry

46 RG received honoraria for participation in advisory boards and speaker fees from Amgen,

47 Janssen, AbbVie, Lilly and Therakos.

48 CP has received grants for his institution from Gilead

49 CS Larsen has received honoraria for participation in advisory boards and research grants from Gilead and

50 speaker fees from Bristol Myer Squibbs.

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ABSTRACT**Background:**

The risk of skin cancer in HIV-infected patients has not been extensively studied.

Objective:

To determine the risk of skin cancer in HIV-infected patients and compare it with the risk in the background population.

Methods:

In a matched, nationwide population-based cohort study we compared the risk of skin cancer in 4280 HIV-infected patients from the Danish HIV cohort study with a background population cohort, according to the level of immunosuppression and route of transmission.

Primary outcomes were time to first basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or malignant melanoma (MM).

Results:

HIV-infected patients had an increased risk of BCC and SCC with IRRs of 1.79 (95% CI 1.43 – 2.22) and 5.40 (95% CI 3.07 – 9.52), respectively, compared with the background population. We observed no increased risk of MM. Low nadir CD4 cell count was associated with an increased risk of SCC. The increased risk of BCC among HIV-infected patients was restricted to men who had sex with men.

Limitations:

Observational design. Small number of patients with melanoma.

Conclusion:

HIV-infected patients have an increased risk of BCC and SCC.. Low nadir, but not current, CD4 cell count as a marker of immunosuppression was associated with an increased risk of SCC.

91 **Key words:**

92 Skin cancer

93 HIV-infection

94 Basal cell carcinoma

95 Squamous cell carcinoma

96 Malignant melanoma

97 Cohort study

98

99 **Capsule Summary:**

100 • The risk of skin cancer may be increased in HIV-infected patients.

101

102 • HIV-infected patients have an increased risk of BCC and SCC. Route of infection is associated with
103 BCC while nadir but not current CD4 cell count is associated with SCC.

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105 • Physicians should be aware of the increased risk of BCC and SCC in HIV-infected patients.

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114 **Background**

115 Skin cancer risk is increased in immunocompromised individuals.^{1,2} After the introduction of highly active
116 antiretroviral therapy (HAART) the overall life expectancy for well-treated HIV-infected patients is
117 approaching that of the background population.³ The immunological recovery resulting from HAART has
118 lowered the incidence of AIDS defining cancers while there is a persistently increased risk of some non-AIDS
119 defining cancers.⁴ Whether HIV-infected patients are at increased risk of skin cancer is not well
120 documented partially since few countries provide reliable information on keratinocyte skin cancers (KSC), in
121 particular basal cell carcinoma (BCC). A two-fold increased risk of BCC and squamous cell carcinoma (SCC)
122 was demonstrated in a study of HIV-infected patients living in the US.⁵
123 In this study, we aim to estimate the risk of non-AIDS defining skin cancer, both KSC (comprising BCC and
124 SCC) and MM in HIV-infected patients compared with a sex- and age matched cohort from the background
125 population as well as siblings of these two cohorts. This unique study design using high quality population-
126 based, nationwide data enabled us to address potential confounding by skin type and family related sun
127 behaviour and to provide data on skin cancer risk in HIV-infected patients from more northern parts of the
128 world.

129

130

131 **Methods**

132 The study was carried out in accordance with The Code of Ethics of the World Medical Association
133 (Declaration of Helsinki). We used four national registries as data sources following approval from the
134 Danish Data Protection Agency. According to Danish law, no human participant committee approval is
135 required for register-based studies.

137 *Setting:*

138 The Danish population consists of 5.7 million inhabitants ⁶ with an estimated adult HIV prevalence of 0.1%.
139 HIV-infected patients are treated in eight specialized HIV centers, and followed on outpatient basis every
140 12–24 weeks. Antiretroviral treatment is provided free of charge to all HIV-infected residents of Denmark.

142 *Data sources:*

143 We used the unique 10-digit civil registration number assigned to all individuals in Denmark ⁷ to link the
144 data sources described below.

146 *The Danish HIV cohort study (DHCS)*

147 The DHCS is a prospective, nationwide, population-based cohort study of all HIV-infected patients aged 16
148 years or older at time of diagnosis, treated at Danish HIV centers from 1 January 1995 with consecutive
149 ongoing enrolment. ⁸ A detailed description of the cohort has previously been published. ⁹ Yearly updates
150 are performed and date of first positive HIV-test and start of antiretroviral treatment (HAART) are
151 important cohort parameters as well as route of infection, CD4 cell counts and HIV RNA measurements.

153 *The Danish Civil Registration System (DCRS)*

154 The DCRS established in 1968 stores information of vital status and demographic data on all Danish citizens.

155 ⁷ We collected date of birth, sex, loss to follow-up and death from this register.

156 *The Danish Cancer register (DCR)*

157 The DCR was established in 1943 and records cancer diagnoses. Cancers are classified according to
158 modified ICD-7 diagnoses from 1943 to 1977 and ICD-10 from 1978 and up. Hospital departments
159 (including pathology), and general practitioners report to the DCR upon first diagnosis of cancer and on
160 change of initial cancer diagnosis. Reporting is mandatory, and the proportion of morphologically verified
161 tumors is 89%.¹⁰ From this register, we collected data on skin cancer diagnosis.

162

163 *Study population/inclusion and exclusion criteria*

164 All HIV-infected patients of Danish origin from the DHCS aged 16 years or more at time of diagnosis were
165 included. For every HIV patient we randomly selected five age- and sex-matched individuals of Danish origin
166 from the background population ("the matched background cohort") being alive and living in Denmark at
167 the date of inclusion. Danish origin was defined as one or both parents being born in Denmark and having
168 Danish citizenship. This restriction by country of origin was applied to reduce potential bias by differences
169 in skin type between HIV-infected patients and the matched background population. Date of inclusion was
170 defined as 1 January 1995, or first date of HIV diagnosis which ever came last. We excluded patients with
171 skin cancer prior to study enrolment.

172 For both HIV-infected patients and the matched background cohort we included siblings in two sibling
173 cohorts. In the DCRS, parents' civil registration number is included for more than 99% of persons born after
174 1952, less in persons born before.¹¹ We included siblings if they had at least one common parent, were
175 alive and living in Denmark at time of study inclusion.

176

177 *Outcome*

178 The primary study outcome was time to first BCC, SCC or MM. We identified the skin cancers by the use of
179 the ICD-10 diagnoses C43.0-C439 (MM) and C44.0-C44.9 (BCC and SCC) coupled with the following

morphology codes; M80902, M80903, M80923, M80933 (BCC) and M80703, M80713, M80743, M80753, M80763 (SCC). SCCs and MM in other locations than the skin were not included.

Statistical analysis

Person-years at risk (PYR) were calculated as time from study inclusion to the date of first cutaneous cancer, death, loss to follow-up, emigration or 31 December 2014, whichever came first.

Incidence rates (IR) with corresponding 95% confidence intervals (CI) were calculated for BCC, SCC and MM. By subtraction, differences in each outcome between the patient and background cohorts were calculated with corresponding 95% CI. Incidence rate ratios (IRRs) of skin cancer for HIV-infected patients compared with the matched background cohort were estimated using Poisson regression models. To address potential association with immunosuppression, we fitted a Poisson regression model for HIV-infected patients only where the following variables were considered: current CD4 cell count below 350 cells/ μ L (time updated variable), ever exposed to HAART (time updated variable), nadir CD4 cell count before study inclusion, sex, and age. As few patients were diagnosed with skin cancer before first treatment with HAART, in the final analysis, we only included HIV-infected patients exposed to HAART. Therefore, we were unable to address the impact of HAART. Consequently, in the final model, IRRs were estimated for current CD4 cell count (<350 versus \geq 350 cells/ μ L), nadir CD4 cell count (per cell/ μ L increase), sex and age (per year increase).

In order to investigate potential confounding from family related factors, in particular the level of sun exposure during childhood and skin type, we compared the risk of skin cancer between siblings of HIV-infected and siblings of the matched background cohort. Further, all analyses were stratified by route of infection (men who have sex with men (MSM) versus other routes of infection), as it has been suggested that HIV-infected MSM have an increased recreational sun exposure.¹² The cumulative incidence function was used to estimate the absolute risk of KSC, with death handled as competing risk.¹³

Results

Of the 6323 HIV-infected patients in the DHCS, we excluded 2043 (32.3%), the majority excluded due to other origin than Danish (Supplementary Figure 1). This left 4280 HIV-infected patients, who were followed for more than 41,000 PYRs. We identified 21,399 individuals for the matched background cohort, followed for more than 274,000 PYRs (Supplementary Figure 1). For descriptive data, see Table 1.

Risk of BCC

The IR of BCC was 2.43 (95% CI: 2.00 – 2.95)/1000 PYR in HIV-infected patient and 1.43 (95% CI: 1.30 – 1.58) /1000 PYR in the matched background cohort with a difference of 1.00 (95% CI: 0.50 – 1.49)/1000 PYR (Table 2).

Figure 1 illustrates the cumulative incidence of BCC. The risk of a BCC diagnosis was increased for the HIV-infected patients (IRR 1.79 (95% CI: 1.43 – 2.22)). Siblings of HIV-infected patients did not have an increased risk of BCC compared with siblings of the matched background cohort (IRR: 1.02 (95% CI: 0.75 – 1.40)). Neither current nor nadir CD4 cell count were associated with risk of BCC (Table 3).

The risk of BCC differed according to route of infection. Those, who reported MSM as the route of HIV-transmission had an increased risk of BCC with IRR of 2.30 (95% CI: 1.76-3.02) compared with the matched background cohort. For other routes of HIV-infection, no increased risk of BCC was observed (Table 2).

Risk of SCC

The IR of SCC was 0.50 (95% CI: 0.32 – 0.77)/1000 PYR in HIV-infected patient and 0.10 (95% CI: 0.07 – 0.15)/1000 PYR in the matched background cohort with a difference of 0.40 (95% CI: 0.18 – 0.62)/1000 PYR (Table 2).

Figure 2 illustrates the cumulative incidence of SCC. The risk of being diagnosed with SCC was increased among HIV-infected patients compared with the matched background cohort with an IRR of 5.40 (95% CI:

229 3.07 – 9.52) (Table 2). We did not detect any difference in risk of SCC when comparing siblings of HIV-
230 infected patients with siblings of the matched background cohort (IRR: 0.70 (95% CI: 0.09 – 5.66)).
231 Nadir, but not current CD4 cell count was associated with a decreased risk of SCC (Table 3).
232 The increased risk of SCC was observed in both MSM as well as HIV patients reporting heterosexual route of
233 HIV transmission (Table 2).

234

235 Risk of MM

236 The risk of developing MM seemed not to be increased among HIV-infected patients (IRR of 0.60 (95% CI:
237 0.28 – 1.31)) or their siblings (IRR of 0.95 (95% CI: 0.55 – 1.61)) when compared with the matched
238 background cohort and siblings of the matched background cohort, respectively. Since all diagnoses of MM
239 among HIV-infected patients appeared when the CD4 cell count was <350 cells/ μ L no further investigation
240 of the impact of immunosuppression was done.

241

242 Discussion

243 In this nationwide, population-based cohort study we observed a two-fold increased risk of BCC and a five-
244 fold increased risk of SCC in HIV-infected patients compared with the background population. The
245 increased risk of BCC was restricted to patients reporting MSM as route of HIV-infection. There seemed to
246 be an association between immunosuppression and SCC-risk for HIV-infected patients. The risk of MM was
247 not increased when compared with the background population but low number of MM cases makes
248 definitive conclusion difficult.

249 One of the main risk factors for developing skin cancer is UV-exposure. In our study, we assumed that skin
250 type and level of sun exposure in childhood were comparable between siblings. We found no increase in
251 BCC-, SCC- or MM-risk among siblings of HIV-infected patients compared with siblings of the matched
252 background cohort; hence, the data did not support confounding by sun exposure in early childhood as an
253 explanation of the increased risk of BCC and SCC among HIV-infected patients.

254 However, since use of sunbeds mostly happens in youth/adulthood, this might differ between siblings.
255 Therefore, an increased risk of KSC in HIV-infected patients, but not their siblings, could be a result of either
256 the immunosuppression caused by the HIV-infection or sunbed use in youth/adulthood. The increased risk
257 of BCC was only seen in patients reporting MSM as route of infection. One could argue that the increased
258 risk of BCC might be driven primarily by sun exposure in youth/adulthood not accounted for by the sibling-
259 model since previous data suggests that HIV-infected MSM might have an increased recreational UV-
260 exposure.¹² Further, no association between BCC and immunosuppression was observed. Difference in
261 lifestyle habits including traveling as well as occupation might also influence the risk; however, data on
262 these parameters were not available for this study.

263 For SCC the picture was somewhat the opposite. SCC seemed to be associated with more severe
264 immunosuppression as reflected by lower nadir CD4 cell count. Further, the increased SCC risk was not
265 restricted to any route of infection. This corresponds to data from other studies in HIV-infected individuals
266 and in solid organ transplant recipients, where the incidence of SCC has been reported to be proportional

267 to the level of immunosuppression.^{5,14,15} Our results were somehow contradictory in terms of CD4 cell
268 count with nadir, but not current CD4 cell count being associated with risk of SCC. We cannot conclude
269 meaningfully on current CD4 cell count due to very wide CI, but it could be hypothesized that nadir CD4
270 count is indicative of immunosuppressive history and represents a time lag between immunosuppression
271 and skin cancer while this exposure lag is not seen with current CD4 cell counts.

272 Human papillomavirus (HPV) alpha is associated with cervical, anogenital-and oropharyngeal cancers. HPV
273 beta has been detected in a proportion of cutaneous SCC, and a possible etiological role has been
274 suggested, especially in the immunosuppressed individuals. However, no mechanism of carcinogenesis has
275 yet been found.^{16,17}

276 A study from California found a 2.6 fold increased risk of SCC and a 2.1-increased risk of BCC when
277 comparing HIV-positive with HIV-negative patients.⁵ The risk of BCC was almost comparable to our results,
278 while the risk of SCC was substantially higher in our study. Numerous factors could affect rates of SCC
279 among both HIV-infected patients and their HIV negative counterparts, which in turn will affect the
280 estimated relative risk of SCC comparing these two groups. In the study from California, SCCs in situ were
281 included. Further, the Californian cohort was older and had a higher CD4 cell count - the latter probably
282 contributes substantially to the lower risk of SCC observed in the American study. Unknown and residual
283 confounding as well as unrecognized interaction between HIV and confounders might also affect the
284 associations found. Finally, differences in sun exposure and skin type between California and Denmark
285 might influence the results though one would expect this to apply for both HIV-infected and controls.

286 Our study was not designed to address the potential effect of skin cancer prevention in HIV-infected
287 patients. In a hypothetical scenario in which prevention reduced the incidence of KSC to that of the
288 background population, the cohort of HIV-infected patients would have to be observed for approximately
289 1000 PYRs to avoid one case of BCC and 2500 PYRs to avoid one case of SCC.

290

291

Major strengths of our study are the nationwide, population-based design with long follow-up, and the high quality and almost complete coverage of Danish registries. Furthermore, potential confounding from family related factors such as skin type and sun exposure in childhood is addressed by comparing siblings. Finally, we matched HIV-infected patients and the matched background cohort on country of origin (Denmark) reducing the potential bias introduced by differences in skin type between the two cohorts. A limitation to our study is reliance on register-based diagnoses without additional validation. A comprehensive assessment has demonstrated that the completeness and validity of the DCR is very high (95-98%).¹⁸ Although including more than 4000 HIV-infected patients with long-term follow-up, we only observed small numbers of SCC and MM, limiting the power of our study and hindering more elaborate stratification. Finally, surveillance bias due to frequent consultations among HIV-infected patients might contribute to the association between KSC and HIV. However, a short-term (positive) association due to diagnostic bias alone would be followed by a later compensatory negative association (e.g., a KSC risk below one during extended follow-up), which was not found. Therefore, we do not believe that diagnostic bias alone explains our findings.

Conclusion

With this nation-wide, population-based cohort study, we have demonstrated that HIV-infected patients have an increased risk of BCC and SCC. Due to few events of MM solid conclusion cannot be made regarding risk of MM in HIV-infected individuals. The risk of SCC seemed to increase with increasing level of immunosuppression while the increased risk of BCC was restricted to patients reporting MSM as route of infection.

314 Abbreviations:

315 HAART: Highly active antiretroviral therapy

316 KSC: Keratinocyte skin cancer

317 BCC: Basal cell carcinoma

318 SCC: Squamous cell carcinoma

319 MM: Malignant melanoma

320 DHCS: The Danish HIV cohort study

321 DCRS: The Danish Civil Registration System

322 DCR: The Danish Cancer register

323 PYR: Person-years at risk

324 IR: Incidence rate

325 CI: Confidence interval

326 IRR: Incidence rate ratios

327 MSM: Men who have sex with men

328 HPV: Human papillomavirus

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References

- 1 Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003; **348**: 1681–91.
- 2 Omland SH, Gniadecki R, Hædersdal M, Helweg-Larsen J, Omland LH. Skin Cancer Risk in Hematopoietic Stem-Cell Transplant Recipients Compared With Background Population and Renal Transplant Recipients: A Population-Based Cohort Study. *JAMA Dermatol* 2016; **152**: 177–83.
- 3 Lohse N, Hansen A-BE, Pedersen G, *et al.* Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann Intern Med* 2007; **146**: 87–95.
- 4 Engels EA, Biggar RJ, Hall HI, *et al.* Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008; **123**: 187–94.
- 5 Silverberg MJ, Leyden W, Warton EM, Quesenberry CP, Engels EA, Asgari MM. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. *J Natl Cancer Inst* 2013; **105**: 350–60.
- 6 Folketal - Danmarks Statistik. <https://www.dst.dk/da/Statistik/emner/befolkning-og-valg/befolkning-og-befolkningsfremskrivning/folketal> (accessed March 9, 2018).
- 7 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014; **29**: 541–9.
- 8 Lohse N, Hansen A-BE, Jensen-Fangel S, *et al.* Demographics of HIV-1 infection in Denmark: results from the Danish HIV Cohort Study. *Scand J Infect Dis* 2005; **37**: 338–43.
- 9 Omland LH, Ahlström MG, Obel N. Cohort profile update: the Danish HIV Cohort Study (DHCS). *Int J Epidemiol* 2014; **43**: 1769–1769e.
- 10 Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health* 2011; **39**: 42–5.
- 11 Christensen K, Schmidt MM, Vaeth M, Olsen J. Absence of an environmental effect on the recurrence of facial-cleft defects. *N Engl J Med* 1995; **333**: 161–4.
- 12 Flegg PJ. Potential risks of ultraviolet radiation in HIV infection. *Int J STD AIDS* 1990; **1**: 46–8.

- 360 13 Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models
361 and competing risks analysis. *Hepatology* 2015; **62**: 292–302.
- 362 14 Jensen P, Hansen S, Møller B, *et al.* Skin cancer in kidney and heart transplant recipients and different
363 long-term immunosuppressive therapy regimens. *J Am Acad Dermatol* 1999; **40**: 177–86.
- 364 15 Gjersvik P, Hansen S, Møller B, *et al.* Are heart transplant recipients more likely to develop skin cancer
365 than kidney transplant recipients? *Transpl Int Off J Eur Soc Organ Transplant* 2000; **13 Suppl 1**: S380–381.
- 366 16 Arron ST, Ruby JG, Dybbro E, Ganem D, Derisi JL. Transcriptome sequencing demonstrates that human
367 papillomavirus is not active in cutaneous squamous cell carcinoma. *J Invest Dermatol* 2011; **131**: 1745–
368 53.
- 369 17 Howley PM, Pfister HJ. Beta genus papillomaviruses and skin cancer. *Virology* 2015; **479–480**: 290–6.
- 370 18 Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry--history, content, quality
371 and use. *Dan Med Bull* 1997; **44**: 535–9.
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- 373

374 **Figure legends**

375 **Figure 1:** The cumulative incidence of basal cell carcinoma (BCC) among HIV-infected patients compared
376 with the matched background population.

377 **Figure 2:** The cumulative incidence of squamous cell carcinoma (SCC) among HIV-infected patients
378 compared with the matched background population.

379

Table 1. Baseline characteristics of HIV-infected patients and the matched background population.

	HIV-infected patients, n= 4280	Age- and sex matched background cohort, n= 21.399	Siblings of HIV- infected patients, n = 5647	Siblings of the background cohort, n = 26.875
Males, n (%)	3641 (85.1)	18.204 (85.1)	3020 (53.5)	14.137 (52.5)
Age at study inclusion, median (IQR)	38.6 (31.7-46.8)	38.6 (31.7-46.8)	34.2 (29.3 – 39.7)	34.5 (29.7 – 39.7)
Route of infection, n (%)				
MSM	2327 (54.4)	n.a.	n.a.	n.a.
Heterosexually	1216 (28.4)	n.a.	n.a.	n.a.
Intravenous drug use	502 (11.7)	n.a.	n.a.	n.a.
Other	235 (5.5)	n.a.	n.a.	n.a.
CD4 cell count at study inclusion (cells/ μ L), median (IQR)	300 (120-504)	n.a.	n.a.	n.a.

Abbreviations: MSM: men who have sex with men, IQR: interquartile range

Table 2. Risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) among HIV-infected patients of Danish origin compared with the matched background population.

		BCC			SCC			MM		
Route of infection		<i>n</i>	Rate per 1000 PYR (95% CI)	IRR (95% CI) *	<i>n</i>	Rate per 1000 PYR (95% CI)	IRR (95% CI) *	<i>n</i>	Rate per 1000 PYR (95% CI)	IRR (95% CI) *
All	HIV-infected patients	101	2.43 (2.00 – 2.95)	1.79 (1.44 – 2.22)	21	0.50 (0.32 – 0.77)	5.40 (3.07 – 9.52)	7	0.17 (0.08 – 0.35)	0.60 (0.28 – 1.31)
	Matched background cohort	392	1.43 (1.30 – 1.58)	Ref.	28	0.10 (0.07 – 0.15)	Ref.	79	0.29 (0.23 – 0.36)	Ref.
MSM	HIV-infected patients	70	3.06 (2.42 – 3.87)	2.30 (1.76 – 3.02)	12	0.52 (0.30 – 0.92)	4.30 (2.10 – 8.82)	4	0.17 (0.07 – 0.47)	0.60 (0.21 – 1.66)
	Matched background cohort	208	1.42 (1.24 – 1.62)	Ref.	20	0.14 (0.09 – 0.21)	Ref.	45	0.31 (0.23 – 0.41)	Ref.
Other	HIV-infected patients	31	1.66 (1.17 – 2.36)	1.18 (0.81 – 1.73)	9	0.48 (0.25 – 0.93)	8.09 (3.12 – 21.00)	3	0.16 (0.05 – 0.50)	0.61 (0.19 – 1.98)
	Matched background cohort	184	1.44 (1.25 – 1.67)	Ref.	8	0.06 (0.03 – 0.13)	Ref.	34	0.27 (0.19 – 0.37)	Ref.

* adjusted for age and sex. Abbreviations: BCC: Basal cell carcinoma, PYR: person years of observation, IRR: incidence rate ratio, CI: confidence interval, SCC: squamous cell carcinoma, MSM: men who have sex with men

Table 3. Risk of BCC and SCC among HIV-infected patients of Danish origin according to current CD4 cell count, nadir CD4 cell count, sex and age.

	IRR (95% CI) for BCC	IRR (95% CI) for SCC
CD4 cell count <350	0.55 (0.28-1.07)	1.12 (0.36-3.46)
CD4nadir (per cell/ μ L increase)	0.999 (0.998-1.009)	0.994 (0.990-0.999)
Sex	2.12 (0.77-5.87)	2.04 (0.27-15.68)
Age (per year increase)	1.07 (1.05-1.10)	1.12 (1.07-1.18)

Abbreviations: IRR: incidence rate ratio, CI: confidence interval



